# Practical use of beta blockers in advanced heart failure

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# Advanced chronic heart failure

- Although patients with chronic HF have improved outcomes with implementation of evidence-based therapies → they still progress to an advanced stage of the disease

- Estimated 1% - 10% of the overall heart failure population

- A thorough definition is mandatory to facilitate appropriate application of treatment (heart transplantation or long-term mechanical circulatory support devices)

Crespo-Leiro MG. Advanced heart failure. EJHF. 2018

# Advanced chronic HF

This definition identifies a group of patients with compromised quality of life, poor prognosis, and a high risk clinical events

These patients deserve effective therapeutic options and should be potential targets for future clinical research initiatives

M. Metra et al. Eur journal of Heart Failure 9 (2007) 684-694.

# Definition

Advanced chronic heart failure defined as a chronic, but not necessarily irreversible, condition

Regardless of its aetiology

# Definition ACHF

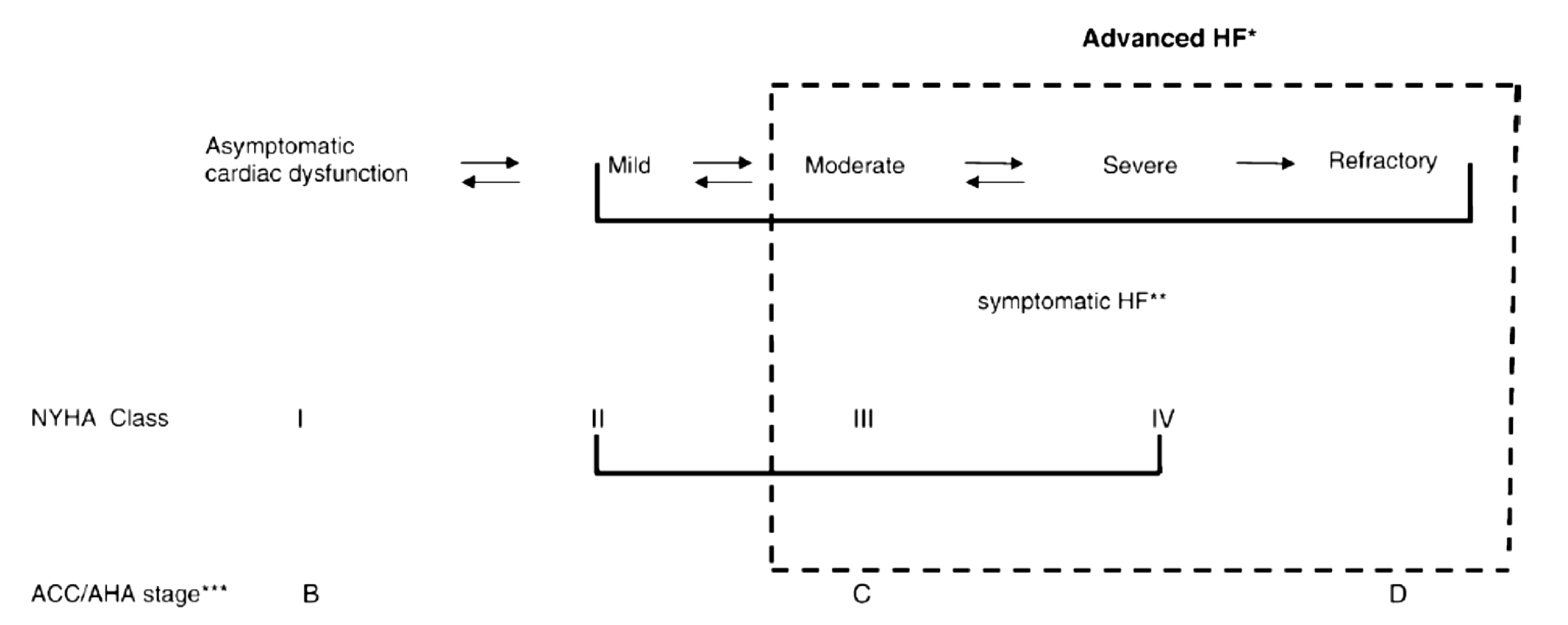
1. Severe symptoms of HF with dyspnea and/or fatigue at rest or with minimal exertion (NYHA class III or IV)
2. Episodes of fluid retention (pulmonary and/or systemic congestion, peripheral oedema) and/or of reduced cardiac output at rest (peripheral hypoperfusion)
3. Objective evidence of severe cardiac dysfunction:
   a. A low LVEF <30%
   b. A severe abnormality of cardiac function on Doppler echo with a psudonormal or restrictive mitral inflow pattern
   c. High LV filling pressures (mean PCWP > 16 mmHg, and/or mean RAP >12 mmHg by pulmonary artery catheterization
   d. Hgh BNP or NT-Pro BNP plasma levels, in the absence of non cardiac causes

M. Metra et al. Eur journal of Heart Failure 9 (2007) 684-694.

# Definition ACHF

4. Severe impairment of functional capacity shown by one of the following:
   a. inability to exercise
   b. 6-MWT distance <300 m or less in females and.or patients aged $\geq$75 years
   c. peak VO2 < 12 to 14 ml/kg/min
5. History of $\geq$1 HF hospitalization in the past 6 months
6. Presence of all the previous features despite "attempts to optimize" therapy including diuretics, inhibitor of RAAS, and beta-blockers, unless these are poorly tolerated or contraindicated, and CRT, when indicated

M. Metra et al. Eur journal of Heart Failure 9 (2007) 684-694.




M. Metra et al. Eur journal of Heart Failure 9 (2007) 684-694.

| Heart Failure Association[4] | American College of Cardiology/American Heart Association[5,6] | Heart Failure Society of America[3] |
|---|---|---|
| 1. Severe symptoms of HF with dyspnoea and/or fatigue at rest or with minimal exertion (NYHA functional class III or IV)<br>2. Episodes of fluid retention (pulmonary and/or systemic congestion, peripheral oedema) and/or of reduced cardiac output at rest (peripheral hypoperfusion)<br>3. Objective evidence of severe cardiac dysfunction, shown by at least one of the following:<br>(a) A low LVEF (<30%)<br>(b) A severe abnormality of cardiac function on Doppler echocardiography with a pseudonormal or restrictive mitral inflow pattern<br>(c) High LV filing pressures (mean PCWP >16 mmHg, and/or mean RAP >12 mmHg by pulmonary artery catheterization)<br>(d) High BNP or NT-proBNP plasma levels, in the absence of non-cardiac causes<br>4. Severe impairment of functional capacity shown by one of the following:<br>(a) Inability to exercise<br>(b) 6MWT distance <300 m or less in females and/or patients aged ≥75 years<br>(c) Peak $VO_2$ <12 to 14 mL/kg/min<br>5. History of ≥1 HF hospitalization in the past 6 months<br>6. Presence of all the previous features despite 'attempts to optimize' therapy including diuretics, inhibitors of the renin–angiotensin–aldosterone system, and beta-blockers, unless these are poorly tolerated or contraindicated, and CRT, when indicated | 1. Repeated (≥2) hospitalizations or ED visits for HF in the past year<br>2. Progressive deterioration in renal function (e.g. rise in BUN and creatinine)<br>3. Weight loss without other cause (e.g. cardiac cachexia)<br>4. Intolerance to ACE inhibitors due to hypotension and/or worsening renal function<br>5. Intolerance to beta-blockers due to worsening HF or hypotension<br>6. Frequent systolic blood pressure <90 mmHg<br>7. Persistent dyspnoea with dressing or bathing requiring rest<br>8. Inability to walk 1 block on the level ground due to dyspnoea or fatigue<br>9. Recent need to escalate diuretics to maintain volume status, often reaching daily furosemide equivalent dose >160 mg/day and/or use of supplemental metolazone therapy<br>10. Progressive decline in serum sodium, usually to <133 mEq/L<br>11. Frequent ICD shocks | The presence of progressive and/or persistent severe signs and symptoms of HF despite optimized medical, surgical, and device therapy. It is generally accompanied by frequent hospitalization, severely limited exertional tolerance, and poor quality of life and is associated with high morbidity and mortality. Importantly, the progressive decline should be primarily driven by the HF syndrome.<br>Indicators of advanced HF in the setting of optimal medical and electrical therapies that should trigger consideration of referral for evaluation of advanced therapies include:<br>• Need for intravenous inotropic therapy for symptomatic relief or to maintain end-organ function<br>• Peak $VO_2$ <14 mL/kg/min or <50% of predicted<br>• 6MWT distance <300 m<br>• ≥2 HF admissions in the last 12 months<br>• >2 unscheduled visits (e.g. ED or clinic) in the last 12 months<br>• Worsening right HF and secondary pulmonary hypertension<br>• Diuretic refractoriness associated with worsening renal function<br>• Circulatory–renal limitation to RAAS inhibition or beta-blocker therapy<br>• Progressive/persistent NYHA functional class III–IV symptoms<br>• Increased 1-year mortality (e.g. 20–25%) predicted by HF survival models (e.g. SHFS, HFSS, etc.)<br>• Progressive renal or hepatic end-organ dysfunction<br>• Persistent hyponatraemia (serum sodium <134 mEq/L)<br>• Recurrent refractory ventricular tachyarrhythmias; frequent ICD shocks<br>• Cardiac cachexia<br>• Inability to perform ADL |

Crespo-Leiro MG. Advanced heart failure. EJHF. 2018

# Further criteria must also be considered

1. Outpatient visits with IV loop diuretics and/or other vasoactive medications are increasingly replacing hospitalization for HF
2. Recurrent malignant arrhythmias are now well recognized contributors to and can be consequences of advanced HF
3. Co-morbidities can complicate the evaluation or patients with advanced HF

Advanced HF : A Position Statement of HFA. EJHF. 2018

# Updated HFA-ESC criteria for defining advanced heart failure

All the following criteria must be present despite optimal guideline-directed treatment:

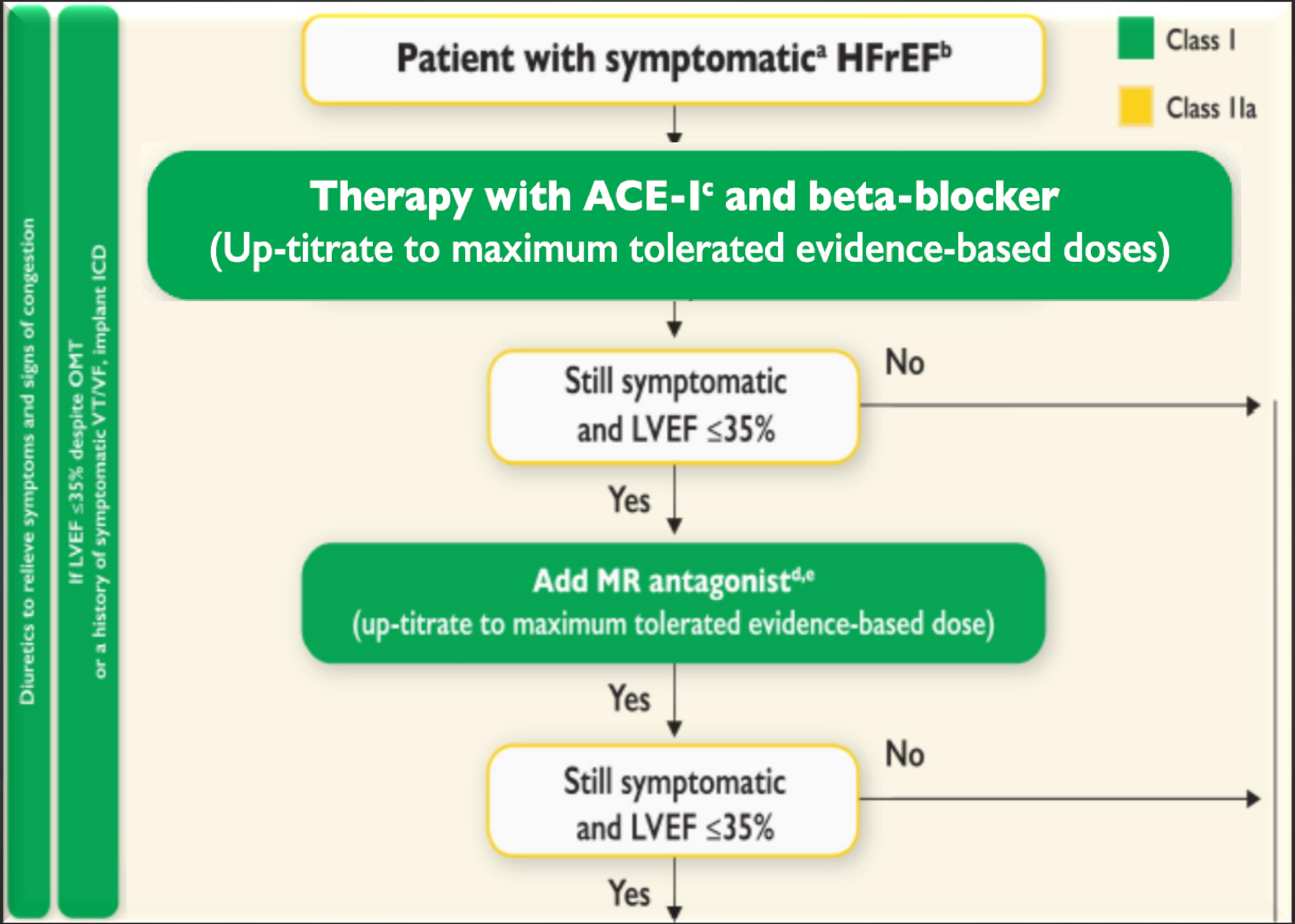
1. Severe and persistent symptoms of heart failure [NYHA class III (advanced) or IV].
2. Severe cardiac dysfunction defined by a reduced LVEF $\leq$30%, isolated RV failure (e.g. ARVC) or non-operable severe valve abnormalities or congenital abnormalities or persistently high (or increasing) BNP or NT-proBNP values and data of severe diastolic dysfunction or LV structural abnormalities according to the ESC definition of HFpEF and HFmrEF.[9]
3. Episodes of pulmonary or systemic congestion requiring high-dose intravenous diuretics (or diuretic combinations) or episodes of low output requiring inotropes or vasoactive drugs or malignant arrhythmias causing >1 unplanned visit or hospitalization in the last 12 months.
4. Severe impairment of exercise capacity with inability to exercise or low 6MWTD (<300 m) or $pVO_2$ (<12–14 mL/kg/min), estimated to be of cardiac origin.

In addition to the above, extra-cardiac organ dysfunction due to heart failure (e.g. cardiac cachexia, liver, or kidney dysfunction) or type 2 pulmonary hypertension may be present, but are not required.

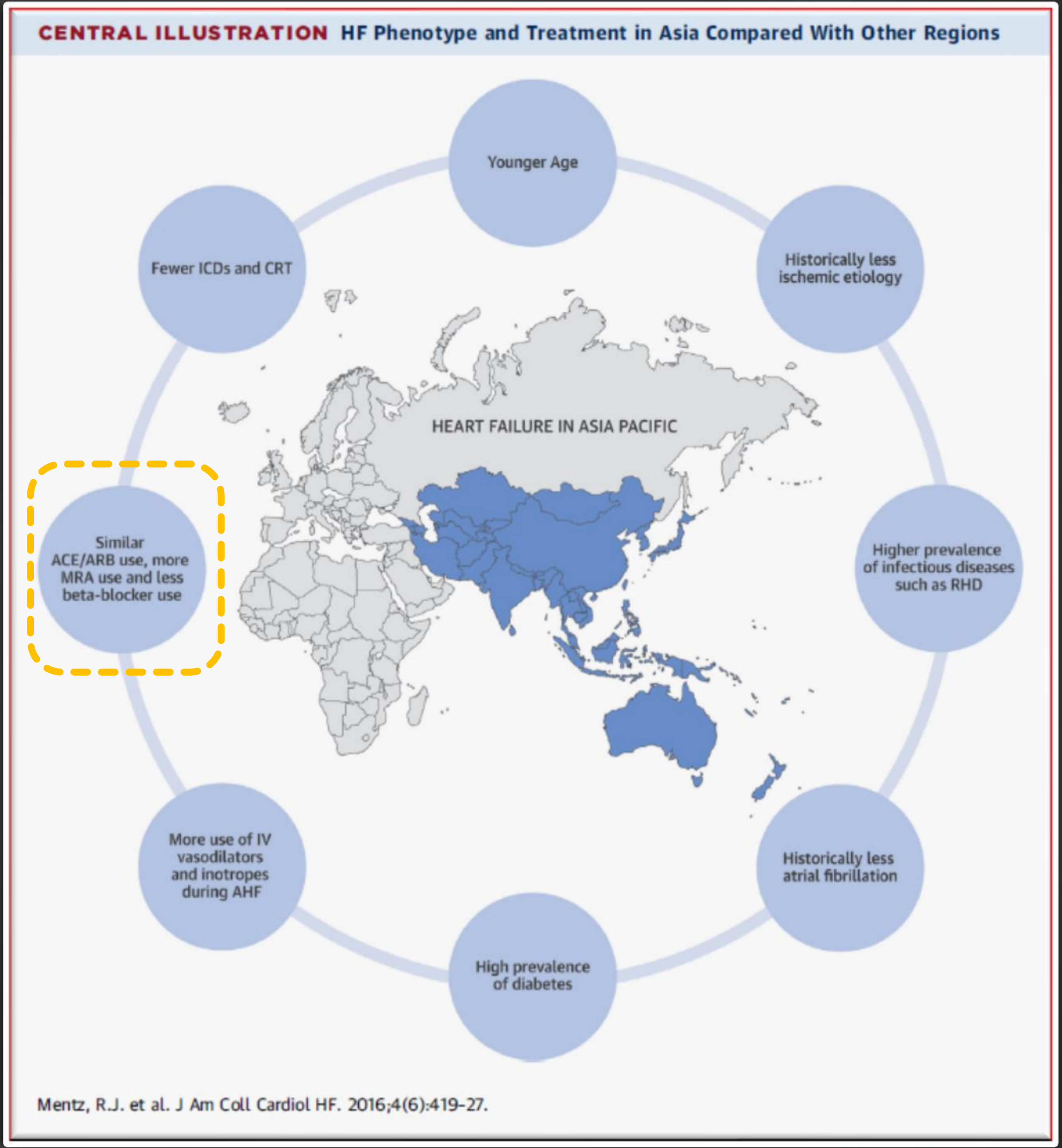
Criteria 1 and 4 can be met in patients who have cardiac dysfunction (as described in criterion #2), but who also have substantial limitation due to other conditions (e.g. severe pulmonary disease, non-cardiac cirrhosis, or most commonly by renal disease with mixed aetiology). These patients still have limited quality of life and survival due to advanced disease and warrant the same intensity of evaluation as someone in whom the only disease is cardiac, but the therapeutic options for these patients are usually more limited.

Advanced HF : A Position Statement of HFA. EJHF. 2018


The
TREATMENT


Patient with symptomatic[a] HFrEF[b]
Class I
Class IIa
Therapy with ACE-I[c] and beta-blocker
(Up-titrate to maximum tolerated evidence-based doses)
Still symptomatic and LVEF ≤35%
No
Yes
Add MR antagonist[d,e]
(up-titrate to maximum tolerated evidence-based dose)
Yes
Still symptomatic and LVEF ≤35%
No
Yes
Diuretics to relieve symptoms and signs of congestion
If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD

# HF phenotype and treatment in Asia



# Diuretics

- The combination of thiazide or spironolactone with loop diuretics has been proposed to overcome diuretic resistance
- The need for continued high dose treatment should be reconsidered once signs of congestion have resolved
- The dose must be adjusted according to the individual needs
- Patients can be trained to self-adjust their diuretic dose

# ACE Inhibitors

- When to start: as soon as possible after diagnosis and exclusion of contraindications
- The benefits of these agents are so important that every effort should be made to use them
- Should be up-titrated to the maximum tolerated dose in order to achieve adequate inhibition of RAAS
- Absolute contraindications includes history of angioneurotic oedema, allergy, pregnancy, and bilateral renal artery stenosis
- Also recommended in asymptomatic LV systolic dysfunction to reduce the risk of HF development, HF hospitalization and death

# ACE Inhibitors

- Low blood pressures (systolic BP <90 mmHg) during ACE-I treatment are acceptable if the patients is asymptomatic
- Moderate renal insufficiency (serum creatinine 3 mg/dL) mild hyperkalemia (<6.0 mmol/L) and relatively low blood pressure (systolic as low as 90 mmHg) are not contraindications → renal function carefully monitored
- If potassium rises to > 6.0 mmol/L or creatinine increase by >50% or to above 3 mg/dL the administration of ACE-I should be stopped

# Angiotensin Receptor Blockers (ARBs)

- Recommended as an alternative in patients who are intolerant of an ACEI
- ARBs may cause worsening renal function, hyperkalemia, and symptomatic hypotension with an incidence similar to ACE-I

# Beta Blockers (BB)

- 1st line treatment (along with ACE-I) in patients with NYHA class II-IV, start as early as possible in course of disease
- Beta-blockade improves ventricular function and patient well-being, reduces hospital admission for worsening HF, and increase survival
- Start low, go slow – in hospital patients

# Beta blockers (BB)

- In patients who develop acutely decompensated HF while on chronic beta-blockers therapy, the dose of these agents may be reduced, or they may be temporarily withdrawn, but treatment should be restarted as soon as clinical conditions stabilize

- Continuation of beta blocker treatment during an episode of decompensation has been shown in an RCT to be safe although dose reduction may be necessary

- Temporary discontinuation is advised in shocked or severely hypoperfused patients

# Who should receive?

- All patients with chronic, stable heart failure
- Without contraindication (Symptomatic hypotension or bradycardia, asthma)

| Setting/indication | Class | Level | Ref. |
|---|---|---|---|
| All stable patients, with symptomatic heart failure and reduced LVEF, functional class II—IV (to prolong survival) | I | A | 55, 108 |
| LVSD without symptoms after AMI | I | A | 55, 108 |
| LVSD without symptoms, no previous MI | I | B | 55 |
| Chronic HF with preserved systolic function (to reduce heart rate) | IIa | C | 108 |
| Acute, compensated heart failure after AMI | IIa | B | 135 |
| Patient stable after acutely decompensated chronic heart failure | I | A | 135 |

ESC Expert consensus document. EHJ 2004

**Table 7.2 Evidence-based doses of disease-modifying drugs in key randomized trials in heart failure with reduced ejection fraction (or after myocardial infarction)**

| Beta-blockers | | |
|---|---|---|
| Bisoprolol | 1.25 *o.d.* | 10 *o.d.* |
| Carvedilol | 3.125 *b.i.d.* | 25 *b.i.d.*[d] |
| Metoprolol succinate (CR/XL) | 12.5–25 *o.d.* | 200 o.d. |
| Nebivolol[c] | 1.25 *o.d.* | 10 *o.d.* |

# When to start?

- No physical evidence of fluid retention
- Start ACEI first (if not contraindicated)
- In stable hospitalized patients (if possible)
- NYHA class IV or severe CHF patients should be referred for specialist advice
- Review treatment, avoid verapamil, diltiazem, antiarrhythmics, NSAID

# Initiation

IMPACT-HF

- Carvedilol initiation pre-discharge was feasible without untoward side effects or prolonged length of stay, and appeared to improve post-discharge beta-blocker use.

OPTIMIZE-HF

- Initiation of beta blocker in the hospital was generally well tolerated and translated to high rates of post discharged use

MERIT-HF

- BB therapy could be safely tolerated in most patients with low risk of deterioration. Risk of deterioration greatest between 4 and 8 weeks of initiation and by week 8 the mortality and hospitalization rates trended in favor of beta-blockade

COPERNICUS

- Clinical benefits on mortality and hospitalizations with beta-blocker therapy

| Therapy<br>First Author (Ref. #) | Study Design | N | Key Results |
|---|---|---|---|
| Beta-blocker | | | |
| Initiation | | | |
| Gattis et al. (3) (IMPACT-HF) | Randomized (open-label) clinical trial: Carvedilol initiation pre-hospital discharge vs. initiation >2 weeks post-discharge at physician discretion | 363 | At 60 days post-randomization, 91% randomized to pre-discharge carvedilol initiation were treated with a beta-blocker, compared with 73% randomized to post-discharge initiation ($p < 0.001$). No difference in rates of serious adverse events or index hospitalization length of stay between groups. |
| Hernandez et al. (5) (OPTIMIZE-HF registry linked to Medicare claims) | Observational: Among patients eligible for beta-blockers, in-hospital beta-blocker initiation vs. no initiation | 3,001 (subset with reduced ejection fraction) | At 1 yr post-discharge, beta-blocker initiation associated with lower adjusted risk for all-cause mortality (HR: 0.77; 95% CI: 0.68-0.87), all-cause rehospitalization (HR: 0.89; 95% CI: 0.80-0.99), and mortality or rehospitalization (HR: 0.87; 95% CI: 0.79-0.96). |

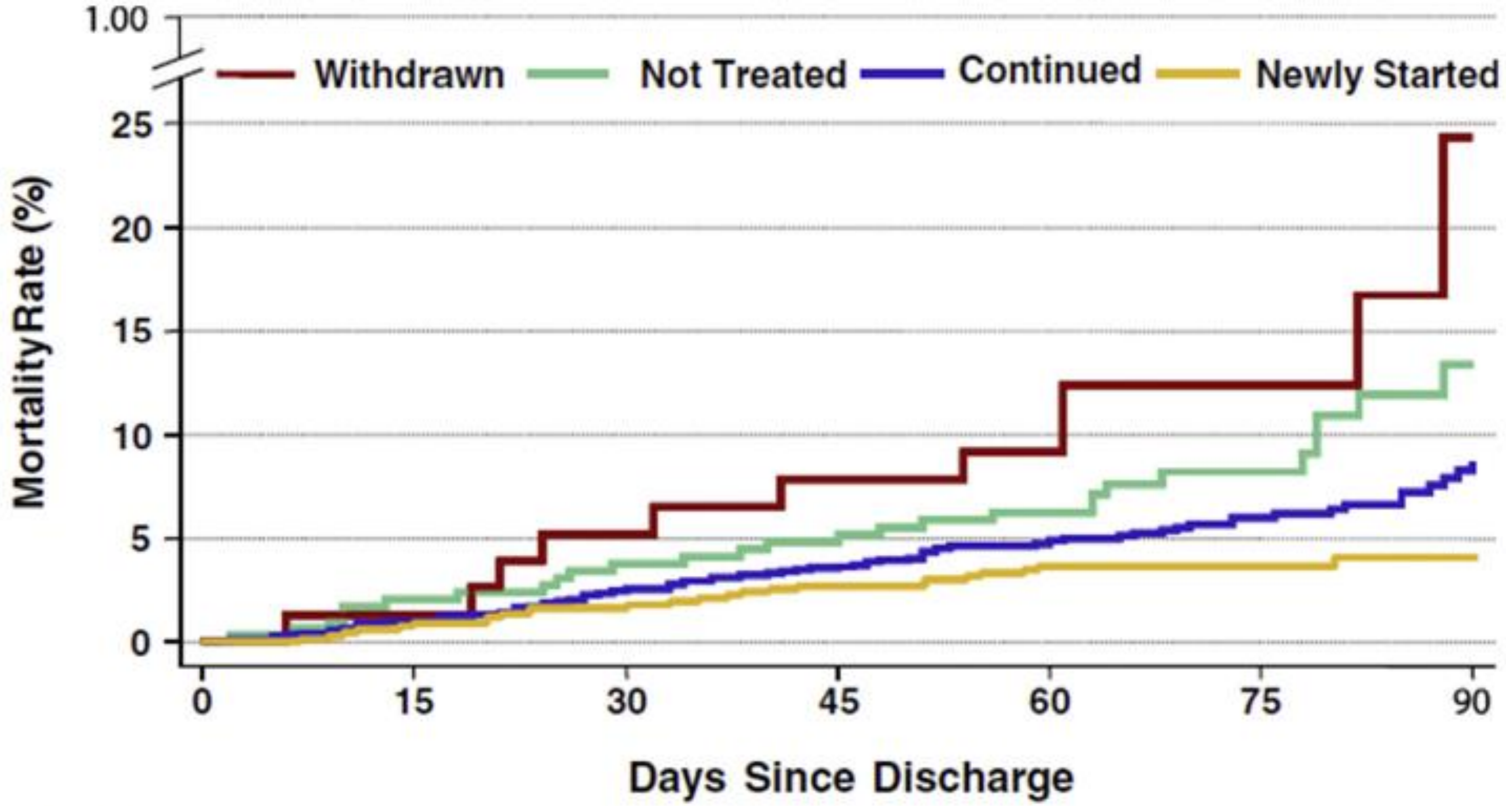
Bhagat et al. In-Hospital Management of Heart Failure Therapies. JACC: Heart Failure vol 7, no. 1. 2019

# Continuation VS Withdrawal

- Continuation of beta-blockers during an acute HF exacerbation in the inpatient setting has been consistently associated with improved clinical outcomes
- OPTIMIZE-HF: those who continued on therapy had a significantly lower risk of post-discharge death and death/rehospitalization compared with patients on no beta-blocker
- Withdrawal of beta-blocker was associated with substantially higher risk-adjusted mortality compared with those who continued.
- Statistically significant benefit of beta-blocker use at discharge (initiation or continuation), showing that death from any cause at 60 to 90 days was lower (6% vs. 11%)

Fonarow GC et al. OPTIMIZE-HF. Am Heart J 2007;153:82

# OPTIMIZE-HF




| Patients at risk: | | | | | | | |
|---|---|---|---|---|---|---|---|
| Withdrawn | 79 | 77 | 73 | 68 | 66 | 26 | 10 |
| Not Treated | 303 | 275 | 269 | 262 | 242 | 114 | 51 |
| Continued | 1350 | 1303 | 1268 | 1236 | 1123 | 536 | 224 |
| NewlyStarted | 632 | 609 | 591 | 575 | 531 | 274 | 110 |

- Lower mortality in patients started on beta-blockers compared with those who were not at 60 to 90 days after discharge.
- 92% of patients continued therapy at 60 to 90 days post-discharge

Fonarow GC et al. OPTIMIZE-HF. J Am Coll Cardiol 2008;52: 190-9

| Therapy<br>First Author (Ref. #) | Study Design | N | Key Results |
|---|---|---|---|
| Continuation or withdrawal | | | |
| Fonarow et al. (7) (OPTIMIZE-HF Registry) | Observational: Among patients eligible for beta-blockers, in-hospital beta-blocker continuation vs. no beta-blocker; beta-blocker withdrawal vs. continuation | 2,373 | At 60-90 days post-discharge, beta-blocker continuation associated with a lower propensity adjusted risk for mortality (HR: 0.60; 95% CI: 0.37-0.99; p = 0.044) and mortality or rehospitalization (odds ratio: 0.69; 95% CI: 0.52-0.92; p = 0.012), compared with no beta-blocker.<br>92% of patients newly initiated on beta-blocker therapy remained on therapy.<br>Beta-blocker withdrawal associated with higher adjusted mortality risk compared with continuation (HR: 2.3; 95% CI: 1.2-4.6; p = 0.013).<br>57% of patients with in-hospital beta-blocker discontinuation were restarted on therapy within 60-90 days. |

Bhagat et al. In-Hospital Management of Heart Failure Therapies. JACC: Heart Failure vol 7, no. 1. 2019

# Switching

- Specific beta-blockers (carvedilol, metoprolol, bisoprolol) have been well studied and proven to improve clinical outcomes in patients with chronic HFrEF.
- Currently, no published studies in hospitalized patients for HFrEF regarding transition from non-evidenced-based beta blockers to evidenced-based beta blockers.
- Clinical experience suggests that transitioning from non-EBM to EBM beta blockers is generally well tolerated in clinically stable hospitalized patients.

Bhagat et al. In-Hospital Management of Heart Failure Therapies. JACC: Heart Failure vol 7, no. 1. 2019

# Safety

- Possible side effects :
  - Bronchospasm
  - Cold peripheries
  - Hypotension
  - Bradycardia
  - ADHF
  - Deterioration in blood glucose control

# Monitoring

- Monitor for evidence of heart failure symptoms, fluid retention, hypotension and bradycardia

- Instruct patients to weigh themselves daily and to increase their diuretic dose if weight increases

# Problem solving

- Reduce / discontinue beta-blocker only if other actions were ineffective to control symptoms / secondary effects

- Always consider the reintroduction and/or uptitration of the beta-blocker when the patient becomes stable

# Problem solving

## Symptomatic hypotension

- Reconsider need for nitrates, calcium channel blockers and other vasodilators
- If no signs/symptoms of congestion consider reducing diuretic dose

## Worsening symptoms/signs

- Double dose of diuretic or/and ACE-I
- Temporarily reduce the dose of beta-blockers if increasing diuretic dose not work
- Review patient in 1 – 2 weeks.
- If serious deterioration halve dose of beta blocker
- Stop beta blocker (rarely necessary)

## Bradycardia

- ECG to exclude heart block
- Consider pacemaker support if severe bradycardia or AV block or sick sinus node early after starting beta-blockers
- Review need, reduce or discontinue other heart rate slowing drugs (digoxin, amiodarone, diltiazem)
- Reduce dose of beta-blocker

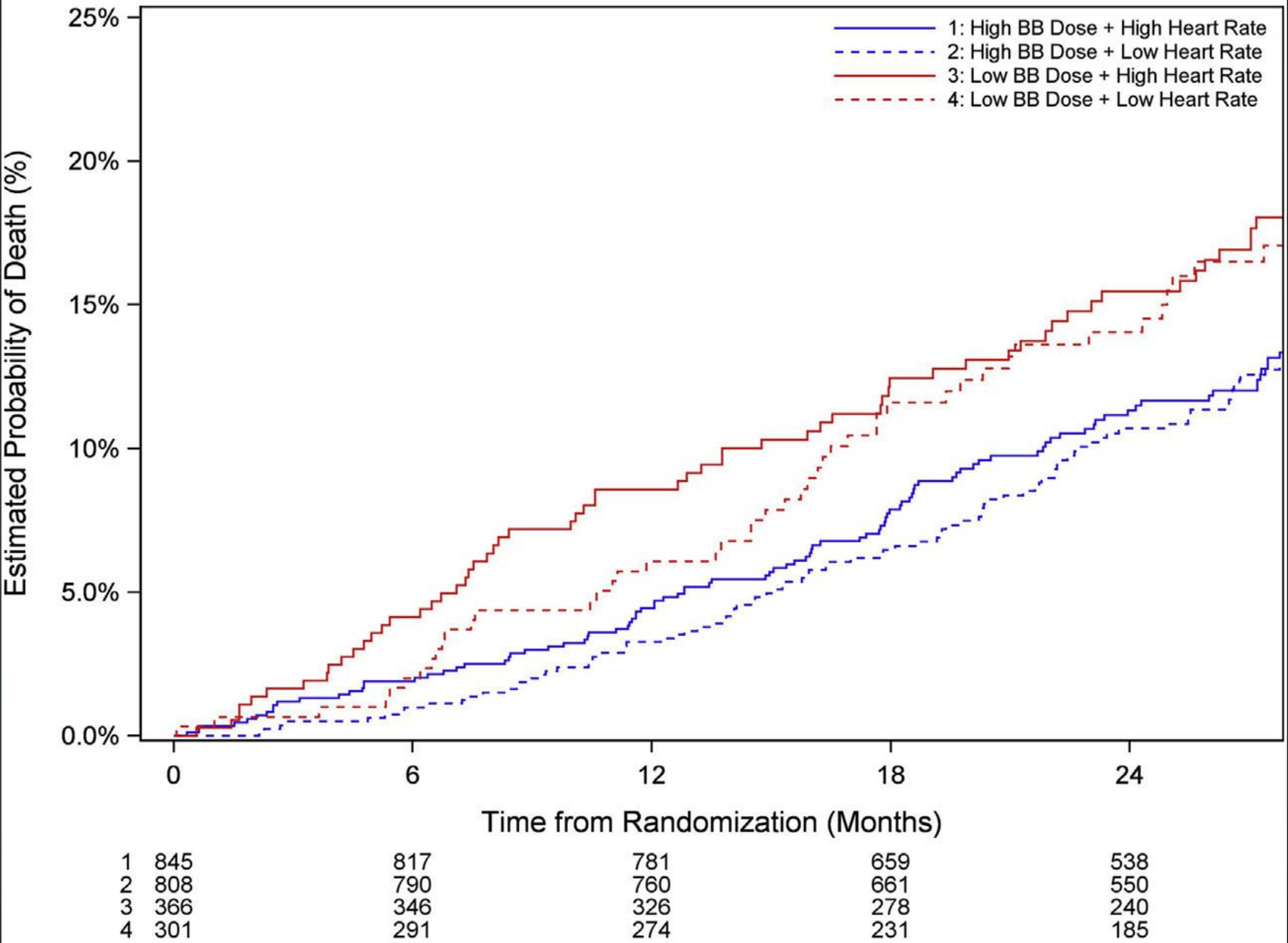
## Severe decompensated HF

- Admit patient to hospital
- Discontinue beta-blocker if inotropic support is needed or symptomatic hypotension/bradycardia is observed
- If inotropic support is needed, levosimendan may ber preferred

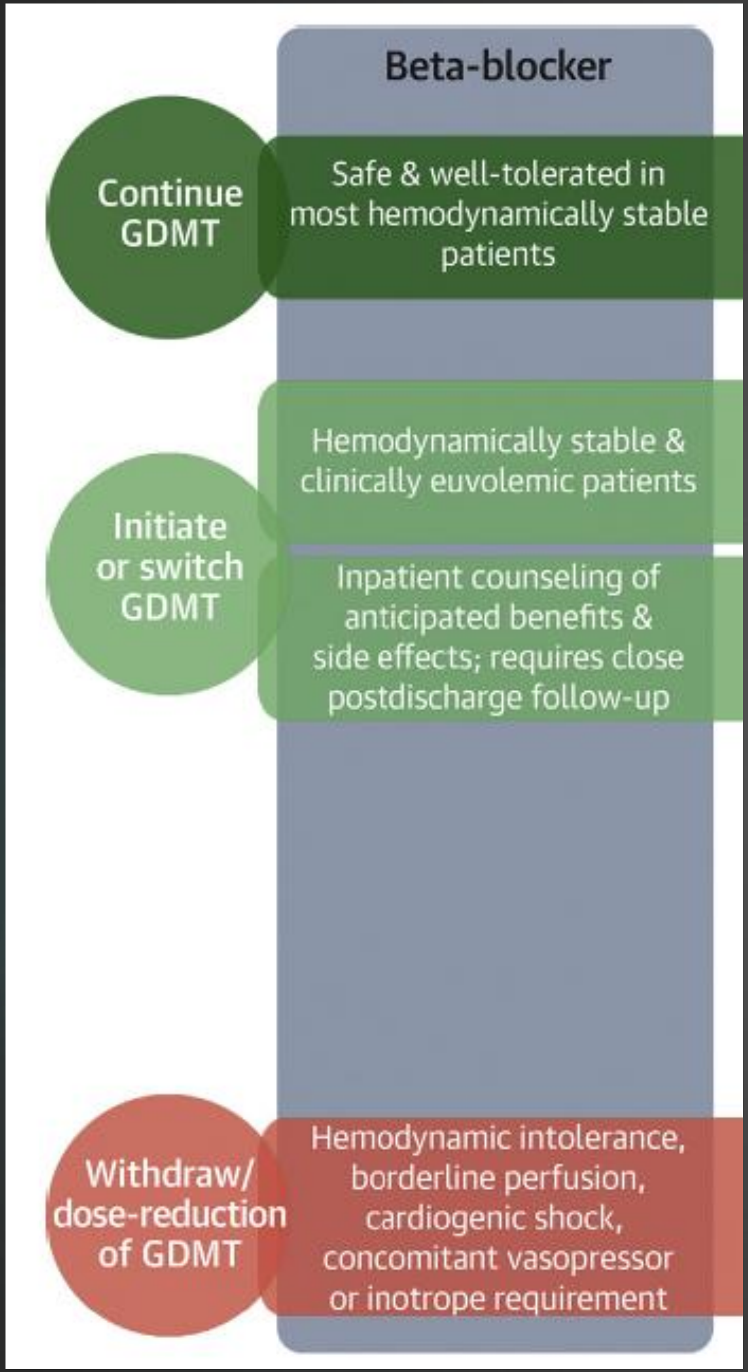
# Conclusion

- HF therapy has improved the survival of heart failure patients, thus they proceed to advanced heart failure stage
- Every effort should be made to reach optimal medication
- Use evidence-based beta blockers (bisoprolol, carvedilol or metoprolol)
- Start with a low dose, increase dose slowly, aim for target dose
- Try not to stop the $\beta$-blocker if the HF deteriorates, try to adjust other drugs to regain control of symptoms and fluid balance


thank you




Fiuzat et al. HF-ACTION Trial. JACC: HEART FAILURE VOL. 4, NO. 2, 2016




**Risks Associated with Failure to Continue/Initiate/Switch GDMT During Hospitalization**

- ↑ risk of readmission & short-, intermediate-, and long-term mortality
- ↓ medication adherence and ↓ medication persistence
- Substantially ↑ likelihood of never being initiated or switched to GDMT as outpatient
- Missing out on the teachable moment during hospitalization

Bhagat, A.A. et al. J Am Coll Cardiol HF. 2019;7(1):1-12.

# Pharmacologic properties of beta-blockers

**TABLE 1 Pharmacologic Properties of Commonly Prescribed β-Blockers**

| Drug | β1/β2 Selectivity (Cardio-Selectivity) | ISA | Half-Life | Additional Properties |
|---|---|---|---|---|
| Second generation | | | | |
| Bisoprolol | ++ | 0 | 9-12 | |
| Metoprolol | ++ | 0 | 3-7 | |
| Atenolol | + | 0 | 6-9 | |
| Third generation | | | | |
| Carvedilol | 0 | 0 | 7-10 | α1-receptor inhibition mediated vasodilation |
| Nebivolol | +++ | 0 | 8-27 | L-arginine/nitric oxide mediated vasodilation |

# Relationship between beta-blockers and clinical outcomes by EF (Meta analysis of 11 RCTs